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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,162	10/31/2002	Mario A Bourdon	LJIEM110-1	8841

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 05/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,162	BOURDON ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *13-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II, Claims 2-12 in the reply filed on March 27, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-29 are all the claims for this application.

Claims 1-12 drawn to a macrophage host cell with species to VEGF are all the claims under examination. Claims 13-29 are withdrawn as being drawn to non-elected subject matter.

Specification

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required. Applicants may wish to consider submitting the Abstract filed with the provisional application, US 60/067591.

Claim Objections

3. Claims 2 and 5 are objected to as being drawn to non-elected subject matter.

4. Claim 6 is objected to for a misspelled word: "stimulation" should be amended to "stimulating".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 4, 5, 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite for the phrase "inhibition of angiogenesis in a cell population" as the claims encompass inhibiting angiogenesis under any condition, e.g., normal (e.g., wound healing), hyperproliferative (e.g., endometriosis), or tumorigenic conditions. It is also unclear how the invention is intended to selectively inhibit aberrant cells as the intended target population.

B) The term "reducing " in the phrase "reducing the activity of a host-cell effecting factor" in claim 4 is a relative term, which renders the claim indefinite. The term "reducing" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The extent to which the activity of the host-cell effecting factor is to be reduced is indefinite. Is this measurable, is there an acceptable range and what is the threshold for a reduced activity?

C) Claim 4 is indefinite for the recitation "wherein said host cell effecting factor, acting alone or in combination with one or more angiogenic factors, potentiates the macrophage angiogenic effect", as it is unclear whether a) the combination of the host cell effecting factor and angiogenic factor act on macrophages to produce a

macrophage angiogenic effect, or b) the host cell factor alone acts on macrophages to produce a macrophage angiogenic effect, which effect on angiogenesis is then potentiated by the angiogenesis factor. In other words, does the method encompass inhibiting both the host cell factor and the angiogenic factor, and does the macrophage angiogenic effect require the presence of an angiogenic factor?

D) Claim 4 recites the limitation "the macrophage angiogenic effect" in line 4. There is insufficient antecedent basis for this limitation in the claim.

E) Claim 4 is indefinite for the recitation "macrophage angiogenic effect" as the phrase encompasses an infinite scope of known and yet to be discovered macrophage-mediated effects on angiogenesis. The specification defines "macrophage angiogenic effect" at p. 5, lines 20-25, to be a "factor released by activated macrophages which functions to produce angiogenesis in tumors in concert with angiogenic factors like VEGF." Later in the specification (p. 17, lines 11-14), Applicants then conclude "the role of macrophages in tumor angiogenesis is not to secrete substances that are directly angiogenic, but rather macrophages are prerequisites for growth factors, such as VEGF to exert its mitogenic effect on endothelial cells."

F) Claim 5 is indefinite in scope for reciting "VEGF" as the term encompasses any protein with this acronym. The full name --vascular endothelial growth factor-- should be inserted to precede the abbreviation.

G) Claim 8 is indefinite for the recitation "is reduced". See the comments under section B), supra, as they apply in the instant case.

H) Claims 8 and 9 are indefinite for the recitation "physically sequestering" as the specification does not define mush less set a standard for how this is achieved. Since the actual operative steps involve anti-M-CSF antibody binding to the substrate M-CSF-1, then perhaps the overall effect of the antagonist would be to neutralize M-CSF-1 activity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a) inhibiting angiogenesis in a tumor cell population for pancreatic carcinoma (e.g., DU145), breast carcinoma (e.g., MCF-7), and rhabdomyosarcoma (e.g., A673) in a mature macrophage-deficient mouse model (NOD/LtSz-scid/scid), b) delaying angiogenesis of a lung cell carcinoma (Lewis Lung cell line (LLC)) in the NOD/LtSz-scid/scid mouse, and c) inhibiting angiogenesis of LLC tumors in the NOD/LtSz-scid/scid mouse by treating with an anti- M-CSF antibody, does not reasonably provide enablement for inhibiting angiogenesis in any cell population much less any tumor cell population in just any mammal with an anti-M-CSF-1 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 1-12 are broadly drawn to inhibiting angiogenesis in any cell population in any mammal comprising inhibiting any macrophage angiogenic effect, which is potentiated by VEGF, using an anti-M-CSF-1 (CSF-1) polyclonal or monoclonal antibody.

Augustin (British J. Radiol. 76:S3-S10 (2003)) provides a recent overview of the state of the art for anti-angiogenic therapies and discusses the successes achieved with Avastatin, the neutralizing VEGF antibody (p. S3, Col. 2, line 10 to S4, line 3; S4, Col. 1, ¶4 to p. S5, Col. 1, ¶1; Figure 2) more especially in treating vascularized tumors. Other therapeutic targeting molecules involved in the angiogenesis cascade are discussed at p. S5, Col. 1, ¶3 to S6, Col. 2, ¶2. Augustin specifically states, however, that:

> "Classical chemotherapy is dependent on the tumour's perfusion for drug delivery. In fact, poor tumour perfusion is one of the primary reasons for the overall poor bioavailability of most chemotherapeutic agents at the tumor site. An antiangiogenic intervention may therefore not be very compatible with classical chemotherapy. Yet, the clinical evidence has shown that the neutralizing VEGF antibody Avastin, which was not effective as a monotherapy, had good efficacy in combination therapy with classical chemotherapy." (p. S8, Col. 2, ¶1)

Thus, even for Avastin, a well characterized and approved therapeutic, anti-angiogenic antibody, Augustin recognizes the limitations in the field of art for practicing immunotherapeutics.

Antibody-based immunotherapeutics are unpredictable in treating ***some*** cancers.

Claims 1-12 encompass inhibiting angiogenesis in tumors or cancers in mammals.

The specification teaches in Examples 1-4 and Figures 1-3 the following: a) inhibiting angiogenesis in a tumor cell population for pancreatic carcinoma (e.g., DU145), breast carcinoma (e.g., MCF-7), and rhabdomyosarcoma (e.g., A673) in a mature macrophage-deficient mouse model (NOD/LtSz-scid/scid), b) delaying angiogenesis of a lung cell carcinoma (Lewis Lung cell line (LLC)) in the NOD/LtSz-scid/scid mouse, and c) inhibiting angiogenesis of LLC tumors in the NOD/LtSz-scid/scid mouse by treating with an anti- M-CSF antibody.

The use of antibody immunotherapy for the treatment of tumors has been shown to have limitations. Jain discloses the art known barriers to the delivery of drugs into solid tumors (Scientific American pp. 58-64 (July 1994)). Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large

therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

Chatterjee et al state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother. 38:75-82 (1994), see Introduction). Results obtained under controlled conditions and in inbred animals, as in the instant specification where nude mice are used as a test animal, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. For example, Dermer states that the widely disparate character of human tumor cells contributes greatly to chemotherapy's continued ineffectiveness against cancer (Biotechnology 12: 320, 1994). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

The specification does not disclose whether the method is effective in animals with pre-existing pancreatic, breast, rhabdomyosarcoma or lung cell tumors, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing all of the method steps, especially the treatment of pre-existing neoplasia, is underscored by Gura et al (Science 278:1041-1042 (1997)) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (p. 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (p. 1042, first-second col, bridging paragraph). One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not correlate with results expected in human patients.

Although monoclonal antibodies have been shown to have specificity for several tumor antigens, and monoclonal antibodies have been able to induce various degrees of tumor immunity for some diseases, few examples have appeared in the application of anti-M-CSF-1 (CSF-1) antibodies as part of immunotherapy to human tumors vis-à-vis the anti-angiogenic effects, it is not clear from the specification whether the anti-M-CSF-1 (CSF-1) antibodies can generate anti-angiogenic responses to all tumors, in all species and to what degree. Furthermore, the examples in the specification rely on a

knock-out mouse with an inherent macrophage deficiency, and given this background of the host mammal, the

Therefore, it appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification alone and the specification fails to enable the use of anti-M-CSF-1 antibodies for inhibiting angiogenesis for just any non-oncogenic or oncogenic cell population.

As evidenced by Seaver (Genetic Engineering 14(14):pages 10 and 21 (1994)), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen. The specification is silent concerning what sort of specificity and affinity would be necessary for the antibodies of the claimed passive immunotherapy so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

Therefore, due the unpredictability of immunotherapeutics in general, and in view of the insufficient guidance and/or working examples concerning the use the claimed antibodies as immunotherapeutic agents, one skilled in the art would not know how to practice the broadly claimed invention, i.e., administering anti-M-CSF-1 antibodies for the inhibition of macrophage-mediated angiogenesis in any cell population and any accompanying pathologies, including affecting tumor-associated angiogenesis without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Nowicki et al. (Int. J. Cancer 65(1):112-119 (January 1996); hereinafter referred to as "Nowicki") as evidenced by Sunderkotter et al. (J. Leukocyte Biol. 55:410-422 (1994); hereinafter referred to as "Sunderkotter").

Claims 1-7 are directed to methods of inhibiting angiogenesis in a cell population in a mammal by inhibiting a macrophage angiogenic effect, wherein the macrophage is subject to regulation by M-CSF (or CSF-1) and by inhibiting the M-CSF, which acts alone or in combination with VEGF to potentiate a macrophage angiogenic effect, the macrophage angiogenic effect is thereby inhibited.

Nowicki discloses that by ablating CSF-1 (M-CSF) expression in a mouse model (op/op mouse), there is a profound decrease in mature cells of the macrophage lineage. In the absence of CSF-1, op/op mice bearing the Lewis lung cancer cell line (LCC) demonstrated less of a tumor burden than normal control littermates (Table 1). More significantly, in the op/op LCC tumor bearing mice, the tumors were less developed, i.e., abortive vessels appeared that were not blood filled and tumors were almost devoid of regular arteries and veins (Figures 3 and 4; p. 118, Col. 1, ¶¶2-3). Nowicki discloses

that CSF-1 dependent macrophages support tumor stroma formation and tumor vascularization in murine LLC tumors (Abstract). Sunderkotter discloses the influences of macrophages at various stages of the angiogenic process and numerous macrophage-derived factors in angiogenesis are listed in Table 1 and explained throughout the text starting at p. 412, Col. 1 to p. 417. Col. 1. Notably, VEGF is one of the angiogenic factors amongst several macrophage angiogenic effects described by Sunderkotter. Thus, inherent to macrophage-mediated LCC tumor angiogenesis are processes involving M-CSF-1 stimulation of macrophages, which act alone or in combination with VEGF, to potentiate a macrophage angiogenic effect.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nowicki et al. (Int. J. Cancer 65(1):112-119 (January 1996); hereinafter referred to as "Nowicki") as evidenced by Sunderkotter et al. (J. Leukocyte Biol. 55:410-422 (1994); hereinafter referred to as "Sunderkotter") and in view of Balakrishna et al. (J. Immunol. 141:483-488 (1988); hereinafter referred to as "Balakrishna").

The interpretation of Claims 1-7 is discussed under section 7, supra. Claims 8-12 are drawn to physically sequestering the M-CSF-1 (CSF-1) molecule with a blocking monoclonal antibody for CSF-1.

Nowicki and Sunderkotter are discussed under section 7, supra. Nowick does not disclose using a monoclonal antibody to inhibit M-CSF-1 (CSF-1) in order to inhibit macrophages from producing an angiogenic effect on a cell population in concert with VEGF.

Balakrishna discloses a Mab produced to purified CSF-1 which neutralizes CSF-1 activity (Figures 2 and 3 and Table II) and use in untangling the roles of CSF-1 in immune modulation and the disease status of the immune system.

It would have been prima facie obvious at the time of the invention to have created the method of inhibiting angiogenesis in a tumor cell population using an anti-M-CSF-1 Mab to inhibit M-CSF-1 from inducing macrophages to express an angiogenic effect in concert with VEGF in view of the combined reference disclosures of Nowicki, Sunderkotter and Balakrishna.

One of skill in the art would have been motivated to have created the method and would also have expected to have achieved a reasonable success in doing so, based on the reference disclosures, because as Nowicki demonstrates in the CSF-1 deficient mouse strain, CSF-1 dependent macrophages play a role in tumor growth and the major role of resident CSF-1-responsive macrophages consists of the promotion of tumour stroma formation and vascularization. Furthermore, Sunderkotter outlines the role of macrophages, especially distinct subtypes of macrophages are capable to provide

several cytokines for the initiation, the maintenance and the termination of the angiogenic process. Accordingly, because of the results achieved in the op/op mouse strain with respect to the significant inhibition of tumor angiogenesis, and the art recognized role of macrophages in the angiogenic process, one skilled in the art could easily and readily modify the method of Nowicki by translating the method into one using anti-angiogenic reagents such as the anti-CSF-1 Mab taught by Balakrishna. Such reagents were readily available, and the impact of inhibiting macrophage angiogenic effects as documented by Nowicki would have rendered the claimed invention obvious.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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